Pentose Phosphate Pathway

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Objectives
Where is it fit in breakdown of glucose?
What its function ?
How its being control ?
What happen when pathway disturb?

Where does the
Pentose Phosphate Pathway
fit into the breakdown of glucose ?
Review the breakdown of Glucose
Where is fit?
It is bypass route around the first step in the glycolytic pathway

Pentose Phosphate Pathway
Is Unique Pathway !!!

No ATP *Produce or Consume*

CO_2 release

Pentose Phosphate Pathway
Two primary product of this pathway:

- Pentose Sugar
- Phosphorylated molecules

Pentose Sugar

Ribose 5 phosphate

Pentose Sugar
- Phosphorylated molecules

NADPH
not
NADH

Redox Pairs

NAD+/NADH= 1000

Donate e^- !
Anabolic reaction involve building up of molecule
e.g. fatty acid synthesis

Use its reducing power to maintain antioxidant store in our body
Reactive Oxygen Species (ROS)
Free Radicals, e.g. the hydroxyl radical •OH
Ions, e.g. the hypochlorite ion ClO^-
Combined Free Radical And Ion,$•O2^-$;

Molecules, e.g. hydrogen peroxide H2O2.

What is Free Radicals

A free radical is any species capable of independent existence with at least one unpaired electron (shown as •) in its outer orbit. Free radicals are very unstable,
short-lived molecules that react rapidly with adjacent molecules causing cellular damage

So how to protect our body ?

Site: Cytosol

Products:

- No ATP directly consumed or produce
- CO_2 release
- Two NADPH is produced for each molecule of glucose – 6 – phosphate

Control

- Rate and direction of the reversible reactions of the pentose phosphate pathway are determined by the supply of and demand for intermediates of the cycle.

Components:

- Oxidative phase
- Non- oxidative phase

Oxidative Phase:

NADPH Production

Ribose – 5- phosphate Production

In this process,

glucose – 6- phosphate is *oxidatively decarboxylated* to ribulose -5 – phosphate.

First Step

Enzyme:

- Glucose -6- Phosphate Dehydrogenase

Action:

oxidize aldehyde at C1 (gluconolactone)
Reduce NADP to NADPH

Control of Process

Regulation: NADPH in potent inhibitor with ratio of NADPH/NADP is high

With increase demand,

the ratio of NADPH/NADP decreases with increase flux through cycle in response to increasing activity of G6PD

Second Step:

Hydrolysis of

Gluconolactone to

6 –phosphogluconate

a sugar acid with carboxyl group at C1

Third Step:

- 6- phosphogluconate dehydrogenase
- Release of CO2

Oxidation of another molecule of NADPH

Ribose – 5- phosphate from oxidative arm:

Ribulose 5- phosphate is isomerized to produce ribose 5 phosphate

Uses:
Enter in nucleotide synthesis
Converted to glycolytic intermediates

Non-oxidative Phase

Need of cell determine the direction of reaction.

If cell had excess of ribose -5- phosphate it will be converted to glycolytic intermediate
If the cell require NADPH, ribose – 5- P will be converted back to glucose 6 phosphate
If the cell already had high NADPH and still need to produce nucleotide the glycolytic intermediates fructose – 6- phosphate and glyceraldehyde 3 phosphate will produce five carbon sugars

Ribose -5- phosphate to glycolytic intermediates:

Enzyme involved
isomerase
epimerase
transketolase
transaldolase

The final result of oxidation of 3 molecule of ribose -5- phosphate
2 molecule of fructose 6 phosphate
1 molecule of glyceraldehyde 3 phosphate

Glycolytic intermediates to Ribose -5- phosphate
When cell require ribose – 5- phosphate for purine and pyrimidine nucleotides
cell synthesize it from glycolytic intermediate

Importance of Pentose Phosphate Pathway
Provide major portion of body NADPH which major biochemical reductant
Provide a source for ribose 5 phosphate for Nucleotide synthesis

Tissue distribution
Liver and mammary gland (which are active in fatty acid synthesis)
Adrenal cortex (NADPH-dependent synthesis of steroids,)
Erythrocytes (NADPH to keep glutathione reduced.)

Uses of NADPH

Reductive biosynthesis
Reduction of hydrogen peroxide
Cytochrome P450 monooxygenase system
Mitochondrial system: hydroxylation of steroid
Microsomal system: detoxification of xenobiotics
Synthesis of nitric oxide
Phagocytosis by white blood cells

Glucose 6 Phosphate Dehydrogenase Deficiency

Glucose 6 phosphate dehydrogenase deficiency

is an inherited disease characterized by hemolytic anemia caused by the inability to detoxify oxidizing agents.

most common disease- producing enzyme abnormality in humans,
- G6PD deficiency is X-linked,
- Shortened red cell life span.

Hydrogen Peroxide
One of reactive oxygen species
formed continuously as by-products of aerobic metabolism
Lead to oxidative stress.
cause serious chemical damage to DNA, proteins, Unsaturated lipids and cell death

How to overcome the effect of Hydrogen peroxide ?

Role of G6PD in RBC

Diminished G6PD activity impairs the ability of the cell to form NAPPH that is essential for the maintenance of the reduced glutathione pool.
Glutathione also helps maintain the reduced states of sulfhydryl groups in proteins, including hemoglobin.
Oxidation of those sulfhydryl groups leads to the formation of denatured proteins that form insoluble masses (called Heinz bodies)
oxidation of membrane proteins causes the red cells to be rigid and non deformable, remove from circulation
Defense against H_2O_2
Enzymes that catalyze antioxidant reactions
Antioxidant chemicals:

Glutathione

a tripeptide-thiol

chemically detoxify hydrogen peroxide
catalyzed by the selenium-requiring Glutathione Peroxidase, forms oxidized glutathione,
cell regenerates reduced glutathione in a reaction catalyzed by glutathione reductase, using NADPH as a source of reducing electrons.

Why defect of G6PD deficiency happen in RBC only ???

Precipitating factors in G6PD deficiency

Oxidant drugs: (AAA)
- Antibiotics (Sulfa)
- Antimalarials
- Antipyretics

Favism:
Infection:
Neonatal jaundice: